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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/759,508	01/12/2001	Mark C. Fishman	00786/381002	2459

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EXAMINER	
SOUAYA, JEHANNE E	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/759,508	Applicant(s) FISHMAN, MARK C.	
	Examiner Jehanne Souaya	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) 8-19 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: 8 .

DETAILED ACTION

Election/Restriction

1. Applicants election without traverse, of Group I, claims 1-7 in Paper No. 13 is acknowledged. Consequently, claims 8-13 have been withdrawn from further consideration as being drawn to a nonelected inventions. An action on the merits of claims 1-7 follows.

Priority

2. Applicants claim for priority to provisional application 60/175,787, filed 1/12/2000 is acknowledged. The claims have been awarded the benefit of the 1/12/2000 filing date as the subject matter in the claims was identically recited in the provisional application. It is noted, however, that the '787 application does not disclose the genotype of the pickwick mutation.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (p. 10). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands,* 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

The claims are broadly drawn to a method for determining whether a test subject from any source, including mammals and humans, has or is at risk of developing *any* titin related disease or condition by detecting *any* mutation from a titin gene. The claims are further drawn to detecting heart failure and to detecting the *pickwick* mutation.

The specification teaches that claimed recitation of a "titin gene" is drawn to a nucleic acid that encodes a titin protein or polypeptide that has 45%, 60%, 75% and 90% identity to the sequence of human or zebrafish titin molecules (see p. 3). Such a recitation encompasses mutants, allelic variants, and homologs of titin from any source, which have not been taught or

described in the specification. The specification further defines "titin related disease or condition" to mean a disease or condition that results from an inappropriately high or low expression of a titin gene or a mutation in a titin gene that alters the biological activity of a titin nucleic acid or polypeptide. Such a recitation encompasses any substitution, deletion or insertion in any titin gene. The specification, however, has only taught a single mutation in the N2B exon of titin that was found in zebrafish embryos characterized with a weak heartbeat (see p. 20). Further, the whereabouts of this mutation in the N2B exon are unclear as the specification only teaches that identification of a T-G transition in the *pikm171* allele was found which resulted in a change of leucine in the IS3 fragment of N2B domain into a stop codon. The specification, however, does not teach at which leucine residue this mutation occurs. In addition, the specification does not define the specific genotype of the *pickwick* mutation. The specification recites "a mutation in a cardiac specific exon, such as the N2B exon, e.g. the *pickwick* mutation" (see p. 2, lines 9-10), thus it is unclear from this recitation or the teachings in the specification as to what is encompassed by the *pickwick* mutation. This recitation, therefore, has been broadly interpreted to encompass any mutation that is responsible for the *pickwick* phenotype (p. 19, lines 4-5). The specification, however, has only taught a single mutation that appears to be associated with a weak heart beat in zebrafish embryos. Such a teaching is insufficient to provide one of skill in the art with a predictable correlation that any substitution, deletion or insertion in the titin gene, or more specifically the IS3 fragment of N2B would result in a weak heartbeat in zebrafish embryos or any other subject. The single point mutation taught in the specification also does not

provide one of skill in the art with a predictable correlation between any mutation in any titin gene from any source and any disease or condition, including heart failure.

The specification lacks sufficient guidance to enable one of skill in the art to make or use the invention as broadly as it is claimed, without undue experimentation. To practice the invention as broadly as it is claimed the skilled artisan would have to perform a large study which included subjects affected with a large number of different diseases or conditions as well as controls and to screen such for any mutation in a titin gene. Such analysis would consist of trial and error research projects, the results of which are unpredictable. It is known for nucleic acids as well as proteins that a single nucleotide or amino acid change or mutation can alter the function of the biomolecule in some instances. The effects of these changes, however, are largely unpredictable as to which ones have a significant effect versus not. The specification has not provided the skilled artisan with any teaching or guidance as to which nucleotide or amino acid positions in the titin gene would be responsible for normal or aberrant activity of the titin protein. Without such, the skilled artisan would further be unable to predictably correlate which mutations would have and would not have an effect on the function or activity of any titin protein.

The art exemplifies such unpredictability with regard to titin mutations as Itoh-Satoh et al (Biochemical and Biophysical Research Communications, vol. 291, pp 385-393; 2002) teach a mutation in the titin gene which may be associated with Dilated Cardiomyopathy (p. 387, col. 2,

lines 7-13), another mutation, Arg328Cys, was found in healthy control subjects, indicating that it is a polymorphism not related with DCM (col. 2, lines 3-5).

Therefore, based on the lack of guidance provided in the specification and the unpredictability taught in the art with regard to an association between a specific mutation in a titin gene and protein and any disease or condition, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it claimed. The skilled artisan would not only be required to screen for a large number of mutations, but would also have to determine whether a statistically significant correlation was present between each mutation and a specific disease or condition. Such would require trial and error analysis, the results of which are unpredictable as exemplified by the teachings of Itoh-Satoh.

Written Description

6. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method for determining whether a test subject from any source, including mammals and humans, has or is at risk of developing *any* titin related disease or condition by detecting *any* mutation from a titin gene. The claims are further drawn to detecting heart failure and to detecting the *pickwick* mutation.

The specification teaches that claimed recitation of a "titin gene" is drawn to a nucleic acid that encodes a titin protein or polypeptide that has 45%, 60%, 75% and 90% identity to the sequence of human or zebrafish titin molecules (see p. 3). Such a recitation encompasses mutants, allelic variants, and homologs of titin from any source, which have not been taught or described in the specification. The disclosure of the single human titin gene and polypeptide in the specification, however, is not representative of the large number of mutants, variants and homologues encompassed by the claimed invention. The specification further defines "titin related disease or condition" to mean a disease or condition that results from an inappropriately high or low expression of a titin gene or a mutation in a titin gene that alters the biological activity of a titin nucleic acid or polypeptide. Such a recitation encompasses any substitution, deletion or insertion in any titin gene. The specification, however, has only taught a single mutation in the N2B exon of titin that was found in zebrafish embryos characterized with a weak heartbeat (see p. 20). Such a teaching is not representative of the large number of substitutions, deletions, and insertions in any titin gene from any source that are encompassed by the claimed invention. Further, single mutation taught is not representative of the large number of mutations that could be responsible for the *pickwick* phenotype. The specification recites "a mutation in a cardiac specific exon, such as the N2B exon, e.g. the *pickwick* mutation" (see p. 2, lines 9-10), thus it is unclear from this recitation or the teachings in the specification as to what is encompassed by the *pickwick* mutation. This recitation, therefore, has been broadly interpreted to encompass any mutation that is responsible for the *pickwick* phenotype (p. 19, lines 4-5). The

specification, however, has only taught a single mutation that appears to be associated with a weak heart beat in zebrafish embryos. The specification provides insufficient written description to support the genus of titin genes or mutations encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

Accordingly, absent a teaching of a representative number of titin nucleic acids and mutations, specification does not provide a written description of the invention of claims 1-7.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Satoh et al (Biochemical and Biophysical Research Communications, vol. 262, pp 411-417, 1999).

With regard to claims 1 and 4-6, Satoh teaches of an A to T transversion in codon 740 of the titin gene of a patient with hypertrophic cardiomyopathy, which replaces an Arginine with Leucine (see abstract). Satoh teaches that this mutation was not found in more than 500 normal chromosomes (see abstract). With regard to claims 2 and 3, Satoh teaches that genomic DNA

was extracted from each subject and that PCR primers flanking each exon of the titin gene were designed to amplify each exon (p. 412-col. 1, "PCR-DCP analysis") and that to identify the mutation in exon 14, the PCR product was cloned into a vector and sequenced (para. bridging cols 1 and 2, p. 412).

9. Claims 1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Jackel et al (FEBS Letters, vol. 408, pp 21-24, 1997).

Jackel teaches that a deletion was found in the Z-line region of the titin gene in a baby hamster kidney cell line (see abstract). Jackel teaches using primer pairs and PCR to amplify genomic titin DNA (see col. 2, section 2.3, p. 21). Since claim 1 only recites a single positive process step, that is analyzing a nucleic acid molecule for a mutation in the titin gene, the teachings of Jackel anticipate the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jäckel et al.

Jäckel teaches that a deletion was found in the Z-line region of the titin gene in a baby hamster kidney cell line (see abstract). Jäckel teaches using primer pairs and PCR to amplify genomic titin DNA (see col. 2, section 2.3, p. 21). Although Jäckel teaches analyzing the mutation using Southern blot analysis, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to sequence the titin gene or fragments to identify a particular mutation. As methods of sequencing to analyze and identify mutations in nucleic acids was readily used in the art at the time the invention was made, one of ordinary skill in the art would have recognized that sequencing would provide an equivalent if not improved method (that is for detecting exact location of deletion, which hybridization analysis may not provide) of mutation analysis.

12. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jäckel et al in view of Satoh et al.

Jäckel teaches that a deletion was found in the Z-line region of the titin gene in a baby hamster kidney cell line (see abstract). Jäckel teaches using primer pairs and PCR to amplify genomic titin DNA (see col. 2, section 2.3, p. 21). Although Jäckel teaches analyzing the mutation using Southern blot analysis, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to sequence the titin gene or fragments to identify a particular mutation. As methods of sequencing to analyze and identify mutations in nucleic acids was readily used in the art at the time the invention was made, as exemplified by

the teachings of Satoh et al (p. 412, para bridging cols 1 and 2), one of ordinary skill in the art would have recognized that sequencing would provide an equivalent if not improved method (that is for detecting exact location of deletion, which hybridization analysis may not provide) of mutation analysis.

Conclusion

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634

May 30, 2002